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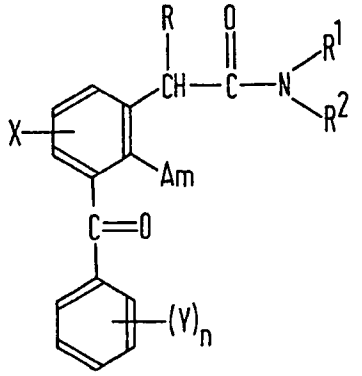
(54) 2-Amino-3-benzoyl-phenylacetamides and cyclic homologues

(57) 2-Amino-3-benzoyl-phenylacetamides are provided having the formula:



wherein:

R represent hdrogen or lower alkyl,

R^1 and R^2 represent hydrogen, lower alkyl, cycloalkyl, phenyl and phenyl substituted by lower alkyl, lower alkoxy, halogen, nitro and trifluoromethyl, and R^1 and R^2 when taken together with the adjacent nitrogen may form a heterocyclic residue;

X represents hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl;

Y represents hydrogen, lower alkyl, lower alkoxy, halogen, trifluoromethyl, lower alkylthio, lower alkyloxythio or lower alkyldioxythio;

Am is primary amino ($-NH_2$), methylamino or dimethylamino, and

n is 1 to 2 inclusive.

The compounds exhibit anti-inflammatory, antipyretic, anti-blood platelet aggregation and analgetic pharmacological activities.

GB 2 059 963 A

Certain of the /The Chemical/ formula(e) appearing in the printed specification was/were submitted after the date of filing, the formula(e) originally submitted being incapable of being satisfactorily reproduced.

SPECIFICATION

2-Amino-3-benzoyl-phenylacetamides and cyclic homologues

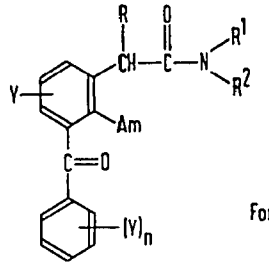
The present invention is concerned with certain novel 2-amino-3-benzoylphenylacetamides and heterocyclic derivatives thereof and pharmacological methods of treatment, therapeutic compositions and use thereof and methods of producing the same. The compounds are anti-inflammatory, antipyretic, analgetic and blood-platelet-aggregation inhibiting agents which exhibit lower undesirable side effects of gastric irritation or oral administration to living animal bodies as compared to prior anti-inflammatory compounds.

2-Amino-3-benzoylphenylacetic acids, esters and metal salts thereof having anti-inflammatory activity and blood-platelet-aggregation inhibiting properties are disclosed in U.S. patent 4,045,576.

South African patent 68/4682 discloses benzoylphenylacetamides generically having a variety of substituents in indefinite positions on the phenyl group. None of the specific compounds disclosed therein are aminophenylacetamides.

Generally, in the past, strong anti-inflammatory drugs have been found to produce serious side effects of gastric bleeding and ulceration when administered orally to animals in the amounts needed for their anti-inflammatory effects to be apparent. The compounds of the present invention have been found to have the advantage that an extremely low incidence of gastric irritation is observed when the compounds are administered in the range of amounts needed to reduce inflammation as compared to indomethacin and the less irritating 2-amino-3-benzoylphenylacetic acids disclosed in U.S. patent 4,045,576.

According to the present invention there is provided 2-amino-3-benzoylphenylacetamides having the following formula, referred to herein as formula I:



Formula I

wherein:

R represents a hydrogen atom or a lower alkyl group;

R^1 and R^2 represent a hydrogen or a halogen atom, a lower alkyl, cycloalkyl, or phenyl group or a phenyl group substituted by a lower alkyl, lower alkoxy, nitro or trifluoromethyl group, and R^1 and R^2 taken together with the adjacent nitrogen atom form a heterocyclic residue;

X represents a hydrogen atom or a halogen atom or a lower alkyl, lower alkoxy, or trifluoromethyl group;

Y represents a hydrogen or a halogen atom or a lower alkyl, lower alkoxy, trifluoromethyl, lower alkylthio, lower alkyloxythio or lower alkyldioxythio group;

Am represents a primary amino ($-NH_2$), methylamino or dimethylamino group, and n is 1 to 3 inclusive.

The novel compounds of Formula I possess valuable pharmacological properties and are useful when administered internally in effective amounts in alleviating inflammation, alleviating pain in an animal afflicted with pain, inhibiting blood-platelet aggregation and combating temperature elevation in living animal bodies, especially mammalian bodies such as is useful in treating fevers, but show lesser side effects which as compared with those of some other strong anti-inflammatory agents are minimal. Illustrative of the anti-inflammatory activity and lower side effects is the compound of Example 3; namely, 2-amino-3-(4-chlorobenzoyl)phenylacetamide which was found to have the same potency as indomethacin but exhibited about only 1/100th as much irritation to the stomach as indomethacin.

The anti-inflammatory activity was demonstrated in laboratory animals using a modification of the Evans-Blue Carrageenan Pleural Effusion Assay of Sancilio, L. F., J. Pharmacol. Exp. Ther. *168*, 199-204 (1969).

The compounds of Formula I exhibit inhibition of platelet aggregation in the test method described by Born, J. of Phys. *162*, 67-68 p. (1962) and Evans et al., J. of Expt. Med. *128*, 877-894 (1968). The test drugs are administered to rats and after two hours the rats are bled and platelet rich plasma obtained. Collagen was added to the platelet rich plasma to induce platelet aggregation and comparisons were made between control and treated samples.

The compounds of Formula I also act as analgetics as determined by the Bradykinin Analgetic Test Method of Dickerson et al., Life Sci. *4*, 2063-2069 (1965) as modified by Sancilio and Cheung, Fed. Proc. *35*, 774 (1976).

Antipyretic activity of the compounds of Formula I is demonstrated in the lowering of the febrile response in hyperthermic animals without affecting the rectal temperature of normothermic animals. Hyperthermic response produced by subcutaneous injection of Brewer's yeast in rats is overcome by oral administration of as little as 4-8 mg/kg of compounds of Formula I and no significant change in rectal temperature of normothermic rats is observed.

In the definitions of symbols in the formulas hereof and where they appear elsewhere throughout this specification, the terms have the following significance.

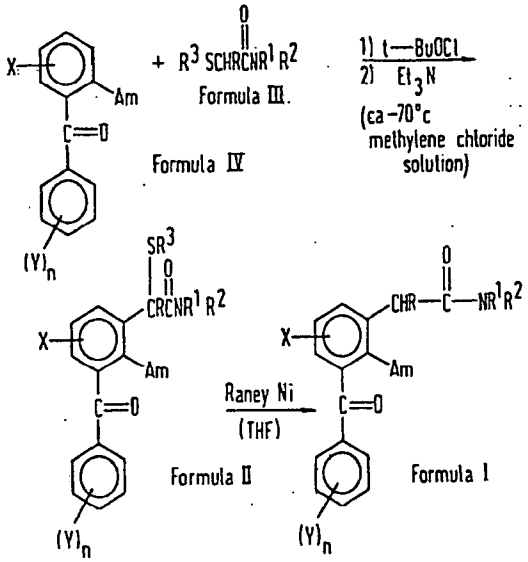
The term "lower alkyl" as used herein means straight and branched chain radicals of up to eight carbon atoms and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, tertiary butyl, amyl, isoamyl, hexyl, heptyl and octyl. The term "lower alkoxy" has the formula -O-lower alkyl.

The term "halogen" when referred to herein means fluorine, chlorine, bromine and iodine. Fluorine, chlorine and bromine are preferred.

The term "cycloalkyl" as used herein means cyclic alkyl radicals containing 3 to 12 carbon atoms inclusive and includes such groups as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

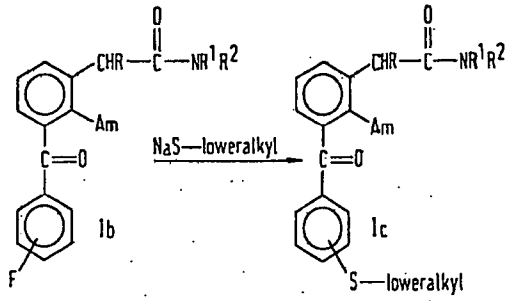
Preferred forms of heterocyclic residue are morpholino, pyrrolidino, piperidino, and piperazino.

The preparation of the compounds of Formula I may be accomplished by reactions which involve the following sequence:

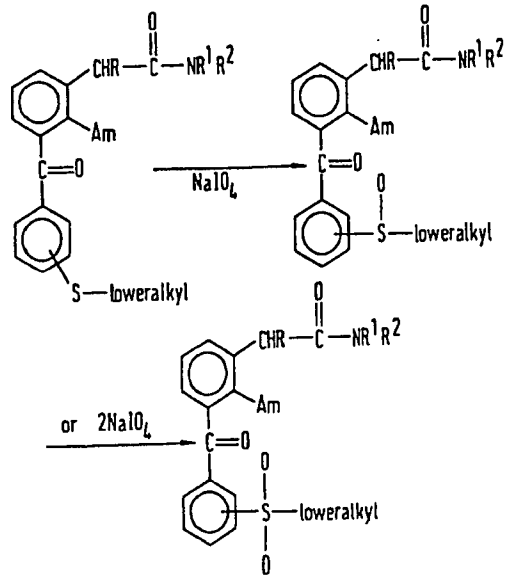


wherein:

R, R^1, R^2, X, Y and n are as hereinabove defined, except Y cannot be a lower alkylthio group or oxides thereof and R^3 is a lower alkyl or phenyl group. Additionally, compounds wherein Y is -S-alkyl are prepared from compounds of Formula I wherein Y is F (fluorine) by the following reaction sequence:



and compounds wherein Y is lower alkyloxythio or lower alkyldioxythio may be prepared by reacting compounds wherein Y is lower alkylthio with 1 or 2 moles of sodium metaperiodate or metachloro perbenzoic acid by the following reaction sequence:



Compounds of Formula I wherein Am is dimethylamino may be prepared by reacting the corresponding 2-amino compound with sodium cyanoborohydride, formaldehyde, acetonitrile and acetic acid.

The preparation of intermediate compounds of Formula II are more fully illustrated in Preparations 6 to 15. Generally, these intermediates are prepared by first reacting the appropriate 2-aminobenzophenones with t-butylhypochlorite and the appropriate thioacetamide in the cold (−60° to −70°C) followed by addition of triethylamine.

The intermediates of Formula II are reduced with Raney nickel to compounds of Formula I in a solvent (except when Y = -S-lower alkyl) such as tetrahydrofuran and isolated by removing the solvent and crystallizing. Compounds of Formula I are prepared as illustrated in the foregoing equation due to interference of Raney Ni on -S-lower alkyl in the reduction step.

PREPARATION 1

4-[2-(Methylthioacetyl)]morpholine

A mixture of 40.2 g (0.3 mole) of ethyl methylthioacetate and 130 g (1.5 mole) of morpholine was heated at reflux for 70 hours. Fractional distillation at reduced pressure gave 45 g (86%) of product b.p. 104-105°C/0.05 mm Hg on second distillation.

Analysis: Calculated for $C_7H_{13}NO_2S$:	C, 47.98;	H, 7.48;	N, 7.99
Found:	C, 47.55;	H, 7.59;	N, 8.18

PREPARATION 2

2-Methylthio-N-methylacetamide

A mixture of 134 g (1.0 mol) of ethyl methylthioacetate and 310 g (10.0 mol) of methylamine was heated in a bomb at 150°C for 72 hours. The excess amine and the ethanol produced were removed by distillation and the remaining thin syrup was distilled to give 112 g (94%) of the titled compound as colorless liquid, b.p. 76° −78°C/0.4 mm Hg.

Analysis: Calculated for C_4H_9NOS:	C,40.31;	H,7.61;	N,11.75
Found:	C,39.78;	H,7.69;	N,11.88

PREPARATION 3

2-Methylthio-N,N-dimethylacetamide

A mixture of 134 g (1.0 mol) of ethyl methylthioacetate and 360 g (8.0 mol) of dimethylamine was heated in a bomb at 150°C for 90 hours. The excess amine and the ethanol produced were removed by distillation and the residue was distilled to give 129 g (97%) of the titled compound as a clear colorless liquid, b.p. 76° −77°C/0.5 mm Hg.

Analysis: Calculated for $C_5H_{11}NOS$:	C,45.08;	H,8.32;	N,10.51
Found:	C,43.88;	H,8.41;	N,10.60

PREPARATION 4

2-(2-Propylthio)acetamide

To a mixture of 46.7 g (0.5 mole) of 2-chloroacetamide in 200 ml of absolute ethyl alcohol was added in a slow stream, a solution of 38.1 g (0.5 mole) of 2-propanethiol in 100 ml of absolute ethyl alcohol and 40 g of

50% aqueous sodium hydroxide. The mixture was heated at reflux for 1 hour, then filtered. The filtrate was concentrated under reduced pressure; the residue was dissolved in methylene chloride and the solution was dried over magnesium sulphate. The mixture was filtered and the filtrate was again concentrated. On standing, the syrupy residue crystallized. Recrystallization from isopropyl ether gave 59.0 g (89%) of white platelets, melting at 52-54°C.

Analysis: Calculated for $C_5H_{11}NOS$:	C,45.08;	H,8.32;	N,10.51
Found:	C,45.05;	H,8.32;	N,10.55

PREPARATION 5

2-(1-Propylthio)acetamide

Utilizing the procedure of Preparation 4 but substituting an equal molar amount of 1-propanethiol for 2-propanethio, there was obtained 61.2 g (92%) of the title compound. The white crystals melted at 49.5-51.0°C.

Analysis: Calculated for $C_5H_{11}NOS$:	C,45.08;	H,8.32;	N,10.51
Found:	C,44.97;	H,8.24;	N,10.40

PREPARATION 6

2-Amino-3-benzoyl-5-chloro-α-(methylthio)phenylacetamide

To a cold (−70°C) solution of 12.77 g (0.055 mole) of 2-amino-5-chlorobenzophenone in 300 ml of methylene chloride, under a nitrogen atmosphere, was added 6.0 g (0.0552 mole) of t-butylhypochlorite in 20 ml of methylene chloride. After an additional 15 minutes stirring period, a suspension of 5.8 g (0.055 mole) of α-(methylthio)acetamide in 150 ml of methylene chloride was added. The mixture was stirred at −65°C for one hour. Triethylamine (5.6 g (0.055 mole)) was added and the solution was allowed to warm to room temperature. The reaction mixture was extracted with several portions of water and the organic layer dried over magnesium sulphate. The volume of solution was reduced *in vacuo* to about 200 ml and the product crystallized as a yellow solid, m.p. 173.5-174.5°C. Yield was 6.86 g (37.3%).

Analysis: Calculated for $C_{16}H_{15}N_2O_2SCl$:	C,57.40;	H,4.52;	N,8;37
Found:	C,57.38;	H,4.50;	N,8.51

PREPARATION 7

2-Amino-3-benzoyl-α-(methylthio)phenylacetamide

To a cold (−70°C) solution of 19.7 g (0.10 mole) of 2-amino-benzophenone in 300 ml of methylene chloride, under a nitrogen atmosphere, was added a solution of 11.5 g (0.10 mole) of 95% t-butylhypochlorite in 30 ml of methylene chloride followed after 10 minutes by a solution of 10.5 g (0.1 mole) of methylthioacetamide in 300 ml of tetrahydrofuran. The temperature was maintained at or below −55°C during these additions. After one additional hour at −60°C the mixture was allowed to warm to room temperature and the precipitate was collected to filtration. The precipitate was slurried in 200 ml of methylene chloride and 11 g (0.11 mole) of triethylamine was added. The mixture was stirred for 5 minutes. The solution was washed twice with 100 ml of water and the organic phase dried over magnesium sulphate and concentrated under reduced pressure. The residue was washed with diethylether and dried to yield 13.0 g (43%) of a light yellow powder, m.p. 153-155°C.

Analysis: Calculated for $C_{16}H_{16}N_2O_2S$:	C,63.98;	H,5.37;	N,9.33
Found:	C,63.64;	H,5.39;	N,9.25

PREPARATION 8

2-Amino-3-(4-chlorobenzoyl)-α-(phenylthio)phenylacetamide

To a cold (−70°C) solution of 34.6 g (0.15 mole) of 2-amino-4'-chlorobenzophenone in 500 ml of methylene chloride was added 17.3 g (0.15 mole) of 95% t-butylhypochlorite, followed after 10 min by a solution of 25.0 g (0.15 mole) of phenylthioacetamide in 400 ml of tetrahydrofuran which was added over a 20 min period. The temperature was maintained at −64°C or below during these additions. After two hours, 20 g (0.2 mole) of triethylamine was added and the mixture was concentrated and the residue partitioned between water and methylene chloride. Material insoluble in either phase was collected by filtration, washed with 20% aqueous ethanol solution and dried to yield 36 g (61%) of light yellow powder, m.p. 189-191°C.

Analysis: Calculated for $C_{21}H_{17}N_2O_2SCl$:	C,63.55;	H,4.32;	N,7.06;
Found:	C,63.73;	H,4.36;	N,7.16

PREPARATION 9

4-[2-(2-Amino-3-benzoylphenyl)-2-(methylthio)acetyl]morpholine

To a cold (−65°C) solution of 9.9 g (0.05 mole) of 2-aminobenzophenone and 8.8 g (0.05 mole) of 4-(α-methylthio)acetylmorpholine (see preparation 1) in 200 ml of methylene chloride was added dropwise a

solution of 5.8 g (0.05 mole) of 95% t-butylhypochlorite in 20 ml of methylene chloride. After one additional hour at −60°C, 5.1 g (0.05 mole) of triethylamine was added and the mixture was allowed to warm to room temperature. The solution was washed twice with 100 ml of water, dried over magnesium sulphate and concentrated under reduced pressure. The residue was chromatographed on 600 g of silica gel eluting first with diisopropylether and finally with 10% acetone in diisopropylether. The eluate was concentrated, the residue dissolved in 150 ml ethanol and the solution poured into 400 ml water. The undissolved solid was collected and crystallized from diethylether and dried. Yield was 12.3 g (62%) of yellow crystals, m.p. 119-121°C.

Analysis: Calculated for $C_{20}H_{22}N_2O_3S$:	C,64.84;	H,5.99;	N,7.56
Found:	C,65.01;	H,5.99;	N,7.57

PREPARATION 10

2-Amino-3-benzoyl-5-chloro-α-[(4-chlorophenyl)thio]-phenylacetamide

To a cold (−70°C) solution of 20 g (0.0863 mole) of 2-amino-5-chlorobenzophenone in 500 ml of methylene chloride under a nitrogen atmosphere was added a solution of 9.48 g (0.088 mole) of t-butyl hypochlorite in 50 ml of methylene chloride. After an additional 15 minutes stirring, a solution of 17.35 g (0.0863 mole) of α-(4-chlorophenylthio)acetamide in 500 ml of a 50/50 mixture of tetrahydrofuran and methylene chloride was added. The mixture was stirred at −70°C for 2 hours, 8.72 g (0.0863 mole) of triethylamine was added, and the stirred solution was allowed to warm to room temperature over a period of 2 hours. The reaction mixture was extracted with several portions of water and the organic layer dried over magnesium sulphate. The volume of liquid was reduced to about 500 ml. Methylene chloride, 500 ml, was added to precipitate the product which after filtration and drying weighed 16.62 g (44.7%). The yellow solid melted at 198-200°C.

Analysis: Calculated for $C_{21}H_{16}N_2O_2SCl_2$:	C,58.48;	H,3.74;	N,6.49
Found:	C,58.49;	N,3.77;	N,6.67

PREPARATION 11

2-Amino-3-benzoyl-5-chloro-α-(phenylthio)phenylacetamide

To a cold (−70°C) solution of 80.72 g (0.349 mole) of 2-amino-5-chlorobenzophenone in 1.5 litre of methylenechloride, under nitrogen atmosphere, was added 39.1 g (0.360 mole) of t-butyl hypochlorite in 100 ml of methylene chloride. After stirring for 10 minutes, a solution of 59.1 (0.354 mole) of α-(phenylthio)acetamide in 1.5 litre of tetrahydrofuran was added. The mixture was stirred for 1.25 hours at −65°C, 37.5 g (0.371 mole) of triethylamine was added and the solution was allowed to warm to room temperature. The reaction mixture was extracted with several portions of water and the organic layer was dried over anhydrous sodium sulphate. The volume of solution was reduced *in vacuo* and a yellow solid precipitated which when recrystallized from acetonitrile was a yellow crystalline solid, m.p. 190-191°C (d).

Analysis: Calculated for $C_{21}H_{17}N_2O_2SCl$:	C,63.55;	H,4.32;	N,7.06
Found:	C,63.62;	H,4.29;	N,7.08

PREPARATION 12

2-Amino-3-benzoyl-α-(phenylthio)phenylacetamide

Following the procedure of Preparation 11 but substituting equal molar amounts of 2-aminobenzophenone for 2-amino-5-chlorobenzophenone the title compound was obtained in 57% yield. Recrystallized from methylene chloride-diethylether-hexane, the compound melted at 153-154°C.

Analysis: Calculated for $C_{21}H_{18}N_2O_2S$:	C,69.59;	H,5.01;	N,7.73
Found:	C,69.33;	H,5.00;	N,7.76

PREPARATION 13

2-Amino-3-benzoyl-α-(methylthio)-N-methylphenylacetamide

A solution of 29.6 g (0.15 mole) of 2-aminobenzophenone in 350 ml of methylene chloride was cooled to −70°C and 17.9 g (0.15 mol) of 2-methylthio-N-methylacetamide (see preparation 2) in 20 ml of methylene chloride was added. To the (−70°C) mixture was added dropwise a solution of 17.2 g (0.15 mole) of 95% t-butylhypochlorite in 30 ml of methylene chloride. The temperature was maintained at or below −65°C for 1.5 hours, then 15.1 g (0.15 mole) of triethylamine was added rapidly. The solution was allowed to warm to room temperature and was washed with water. The organic solution was concentrated and the residue crystallized when mixed with isopropyl ether. The solid was recrystallized from isopropyl alcohol to give 31 g (65%) of yellow needles, m.p. 149.0-150.0°C.

Analysis: Calculated for $C_{17}H_{18}N_2O_2S$:	C,64.94;	H,5.77;	N,8.91
Found:	C,65.24;	H,5.83;	N,8.99

PREPARATION 14

2-Amino-3-benzoyl-α-(methylthio)-N,N-dimethylphenylacetamide

A solution of 29.6 g (0.15 mole) of 2-aminobenzophenone in 350 ml of methylene chloride was cooled to −70°C and 20.0 g (0.15 mole) of 2-methylthio-N,N-dimethylacetamide (see preparation 3) was added. To the mixture (−70°C) was added dropwise a solution of 17.2 g (0.15 mole) of 95% t-butylhypochlorite in 30 ml of methylene chloride. The temperature was maintained at or below −65°C for 1.5 hour, then 15.1 g (0.15 mole) of triethylamine was added rapidly. The solution was allowed to warm to room temperature and was washed with water. The organic solution was concentrated and the residue crystallized when mixed with isopropyl ether. The solid was recrystallized from isopropyl alcohol to give 39.8 g (81%) of bright yellow crystals, m.p. 153-155°C.

Analysis: Calculated for $C_{18}H_{20}N_2O_2S$:	C,65.83;	H,6.14;	N,8.53
Found:	C,65.87;	H,6.15;	N,8.52

PREPARATION 15

2-Amino-3-(4-fluorobenzoyl)-α-(n-propylthio)phenylacetamide

A solution of 21.5 g (0.1 mole) of 4'-fluoro-2-aminobenzophenone in 400 ml of methylene chloride was cooled to −70°C and 11.5 g (0.1 mole) of 95% t-butyl-hypochlorite was added over a period of 15 minutes, keeping the temperature below −66°C. To this solution was added a solution of 13.3 g of 2-n-propylthioacetamide (see preparation 4) in 50 ml of methylene chloride over a 10 minute period. The solution was stirred for 1 hour at −65° to −70°C and then allowed to warm to 0°C at which point 10.2 g (0.1 mole) of triethylamine was added. The solution was stirred for 10 minutes and then washed with water. The organic solution was dried over magnesium sulphate. After concentrating under reduced pressure, the residue was crystallized from isopropyl alcohol and dried to give 19.5 g (56%) of yellow crystals melting at 140-142°C.

Analysis: Calculated for $C_{18}H_{19}N_2O_2SF$:	C,62.41;	H,5.53;	N,8.09
Found:	C,62.34;	H,5.58;	N,8.04

PREPARATIONS 16A TO 16D

In the same manner as given in preparation 8,
2-amino-3-(2-fluorobenzoyl)-α-(phenylthio)phenylacetamide,
2-amino-3-(4-trifluoromethylbenzoyl)-α-(phenylthio)phenylacetamide,
2-amino-3-(2,4-dichlorobenzoyl)-α-(phenylthio)phenylacetamide, and
2-amino-3-(2,4-difluorobenzoyl)-α-(phenylthio)phenylacetamide,
are prepared from phenylthioacetamide, t-butylhypochlorite, and
2-amino-2'-fluorobenzophenone,
2-amino-4'-trifluoromethylbenzophenone,
2-amino-2',4'-dichlorobenzophenone, and
2-amino-2',4'-difluorobenzophenone

PREPARATION 17

2-Amino-3-benzoyl-5-chloro-α-(methylthio)-N-methylphenylacetamide

To a solution of 38.3 g (0.166 mole) of 2-amino-5-chlorobenzophenone in 1 litre of methylene chloride cooled to −70°C under an atmosphere of nitrogen was added 18.05 g (0.167 mole) of t-butylhypochlorite. The solution was stirred for 15 minutes and then a solution of 20.3 g (0.171 mole) of 2-methylthio-N-methylacetamide (see preparation 2) in 100 ml of methylene chloride was added. The solution was stirred at −70°C for 2 hours and 25 ml of triethylamine was added. While stirring, the solution was allowed to warm to room temperature followed by extraction with water and drying of the organic layer with magnesium sulphate. The volume of the solution was reduced to about 400 ml, ether was added and the solution placed in a refrigerator at about 0°C overnight. The solid which crystallized was dried under high vacuum for about 4 hours at 50°C. The weight of the product was 31.56 g (54.6%) and the product melted at 170-171°C.

Analysis: Calculated for $C_{17}H_{17}N_2O_2SCl$:	C,58.53;	H,4.91;	N,8.03
Found:	C,58.68;	H,4.91;	N,8.13

PREPARATION 18

3-Benzoyl-2-(N-methylamino)-α-(methylthio)phenylacetamide

When in accordance with the procedure of preparation 7, 2-N-methylaminobenzophenone is substituted in equimolar amount for 2-aminobenzophenone, the title compound is obtained.

EXAMPLE 1

2-Amino-3-benzoyl-5-chlorophenylacetamide

A mixture of 21.34 g (0.0639 mole) of 2-amino-3-benzoyl-5-chloro-α-(methylthio)-phenylacetamide (see preparation 6) and excess Raney nickel in a mixture of 900 ml of absolute ethanol and 200 ml of

dimethylformamide was stirred at room temperature for 45 minutes. The mixture was filtered through Celite (Registered Trade Mark) to remove the Raney nickel. The solvent was removed *in vacuo* to give a yellow solid which when recrystallized melted at 213.5-215.0°C (d).

Analysis: Calculated for $C_{15}H_{13}N_2O_3Cl$:	C,62.40;	H,4.54;	N,9.70
Found:	C,62.35;	H,4.58;	N,9.74

EXAMPLE 2

2-Amino-3-benzoyl-phenylacetamide

To an agitated solution of 9.7 g (0.032 mole) of 2-amino-3-benzoyl-α-(methylthio)-phenylacetamide (see preparation 7) in 100 ml of tetrahydrofuran was added 80 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran). After 10 minutes the mixture was filtered to remove Raney nickel and the filtrate concentrated under vacuum. The residue was crystallized from isopropyl alcohol to give 6.0 g (73%) of yellow needles, m.p. 178.5-180.0°C.

Analysis: Calculated for $C_{15}H_{14}N_2O_2$:	C,70.85;	H,5.55;	N,11.02
Found:	C,70.53;	H,5.53;	N,11.04

EXAMPLE 3

2-Amino-3-(4-chlorobenzoyl)phenylacetamide

To an agitated solution of 28.5 g (0.077 mole) of 2-amino-3-(4-chlorobenzoyl)-α-(phenylthio)phenylacetamide (see preparation 8) in 1 litre of tetrahydrofuran was added 230 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran). After 15 minutes the mixture was filtered and the filtrate concentrated under reduced pressure to give 17.4 g (84%) of yellow crystalline solid. Recrystallization from isopropyl alcohol followed by recrystallizing twice from absolute ethanol gave yellow needles, m.p. 212-215°C.

Analysis: Calculated for $C_{15}H_{13}N_2O_2Cl$:	C,62.40;	H,4.54;	N,9.70
Found:	C,62.76;	H,4.58;	N,9.83

EXAMPLE 4

4-[2-(2-Amino-3-benzoylphenyl)acetyl]morpholine

To an agitated solution of 18.5 g (0.05 mole) of 4-[2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetyl] morpholine (see preparation 9) in 300 ml of tetrahydrofuran was added 150 g of wet Raney nickel. After 15 minutes the mixture was filtered and the filtrate concentrated under reduced pressure. After recrystallization of the residue from isopropyl alcohol, there was obtained 13.3 g (82%) of bright yellow crystals, m.p. 156.5-158.5°C.

Analysis: Calculated for $C_{19}H_{20}N_2O_3$:	C,70.35;	H,6.22;	N,8.64
Found:	C,70.24;	H,6.21;	N,8.63

EXAMPLE 5

2-Amino-3-benzoyl-N-methylphenylacetamide

A solution of 22.5 g (0.072 mol) of 2-amino-3-benzoyl-α-(methylthio)-N-methylphenylacetamide (see preparation 13) in 400 ml of tetrahydrofuran was treated with 160 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran) for 10 minutes. The mixture was filtered and the filtrate was concentrated. The residue was crystallized from isopropyl alcohol to give 17.2 g (89%) of yellow needles, m.p. 145-146°C.

Analysis: Calculated for $C_{16}H_{16}N_2O_2$:	C,71.62;	H,6.01;	N,10.44
Found:	C,71.76;	H,6.05;	N,10.52

EXAMPLE 6

2-Amino-3-benzoyl-N,N-dimethylphenylacetamide

A solution of 33.0 g (0.1 mol) of 2-amino-3-benzoyl-α-(methylthio)-N,N-dimethylphenylacetamide (see preparation 14) in 500 ml of tetrahydrofuran was treated with 240 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran) for 10 minutes. The mixture was filtered and the filtrate was concentrated. The residue was crystallized from isopropyl alcohol to give 27.2 g (96%) of yellow needles, m.p. 123-124°C.

Analysis: Calculated for $C_{17}H_{18}N_2O_2$:	C,72.32;	H,6.43;	N,9.92
Found:	C,72.34;	H,6.42;	N,9.98

EXAMPLE 7

2-Amino-3-(4-fluorobenzoyl)-phenylacetamide

A solution of 24.2 g (0.07 mole) of 2-amino-3-(4-fluorobenzoyl)-α-(n-propylthio)phenylacetamide (see preparation 15) in 300 ml of tetrahydrofuran was treated with 250 g of wet Raney nickel (washed 3 times with water and 3 times with tetrahydrofuran). The mixture was stirred for one hour and filtered. The filtrate was concentrated under vacuum and the residue was recrystallized from 95% ethyl alcohol to give 14.8 g (78%) of yellow needles melting at 184-186°C.

Analysis: Calculated for $C_{15}H_{13}N_2O_2F$:	C,66.17;	H,4.81;	N,10.29
Found:	C,66.32;	H,4.81;	N,10.48

EXAMPLES 8A TO 8D

In the same manner as given in Example 2,
2-amino-3-(2-fluorobenzoyl)phenylacetamide, (Example 8A),
2-amino-3-(2,4-dichlorobenzoyl)phenylacetamide, (Example 8B),
2-amino-3-(2,4-difluorobenzoyl)phenylacetamide, (Example 8C), and
2-amino-3-(4-trifluoromethylbenzoyl)phenylacetamide (Example 8D) are prepared from
2-amino-3-(2-fluorobenzoyl)-α-(phenylthio) phenylacetamide, (see preparation 16A)
2-amino-3-(2,4-dichlorobenzoyl)-α-(phenylthio) phenylacetamide, (see preparation 16C)
2-amino-3-(2,4-difluorobenzoyl)-α-(phenylthio) phenylacetamide, (see preparation 16D), and
2-amino-3-(4-trifluoromethylbenzoyl)-α-(phenylthio)-phenylacetamide, (see preparation 16B).

EXAMPLE 9

2-Amino-3-(4-methylthiobenzoyl)phenylacetamide

The title compound is prepared by refluxing 2-amino-3(4-fluorobenzoyl)phenylacetamide with excess sodium methyl mercaptide in ethanol and isolated by suitable means.

EXAMPLE 10

2-Amino-3-(4-oxymethylthiobenzoyl)phenylacetamide

The title compound is prepared by reacting one mole of 2-amino-3-(4-methylthiobenzoyl)phenylacetamide with one mole of sodium metaperiodate and isolated by suitable means.

EXAMPLE 11

2-Amino-3-(4-dioxymethylthiobenzoyl)phenylacetamide

The title compound is prepared by reacting one mole of 2-amino-3-(4-methylthiobenzoyl)phenylacetamide with two moles of sodium metaperiodate and isolated by suitable means.

EXAMPLE 12

2-Amino-3-benzoyl-5-chloro-N-methylphenylacetamide

A solution of 28.33 g (0.081 mole) of 2-amino-3-benzoyl-5-chloro-α-(methylthio)-N-methylphenylacetamide (see preparation 17) in one litre of tetrahydrofuran was treated with excess Raney nickel at room temperature for 2 hours. The solution was filtered through Celite (Registered Trade Mark). The Raney nickel residue was washed with acetone and the wash liquids filtered. The combined organic filtrates were dried over magnesium sulphate and the volume reduced to about 300 ml. Excess ether was added and the solution allowed to stand at room temperature for one hour followed by refrigeration overnight. The yellow solid was collected and dried and weighed 20.94 g (85.68%) and melted at 179-180°C.

Analysis: Calculated for $C_{16}H_{15}N_2O_2Cl$:	C,63.48;	H,4.99;	N,9.25
Found:	C,63.44;	H,4.99;	N,9.27

EXAMPLE 13

3-Benzoyl-2-(N-methylamino)-phenylacetamide

When in the procedure of Example 2, 3-benzoyl-2-(N-methylamino)-α-(methylthio)phenylacetamide is substituted for 2 amino-3-benzoyl-α-(methylthio)phenylacetamide, the title compound is obtained.

EXAMPLE 14

3-Benzoyl-2-(N,N-dimethylamino)-phenylacetamide

A solution of 12.7 g (0.05 mol) of 2-amino-3-benzoyl-phenylacetamide in 150 ml of acetonitrile is treated four times with 16 ml (0.2 mole) of 37% formalin, 6.4 g (0.1 mole) of sodium cyanoborohydride and 2 ml of glacial acetic acid with a 15 minute stirring period between each treatment. The mixture is finally poured into dilute sodium hydroxide and extracted three times with diethylether. The ether extracts are combined, dried over magnesium sulphate and concentrated. The product is isolated by column chromatography.

The present invention also extends to novel therapeutic compositions containing the compounds of the invention as active ingredients. Effective quantities of any of the foregoing pharmacologically active compounds may be administered to a living animal body in any one of various ways, for example, orally as

in capsules or tablets, parenterally in the form of sterile solutions or suspension, and in some cases intravenously in the form of sterile solutions. In forming the novel compositions of this invention, the active ingredient is incorporated in a suitable carrier, illustratively, a pharmaceutical carrier. Suitable pharmaceutical carriers which are useful in formulating the compositions of this invention include starch, gelatin, glucose, magnesium carbonate, lactose, and malt. Liquid compositions are also within the purview of this invention and suitable liquid pharmaceutical carriers include ethyl alcohol, propylene glycol, glycerine, and glucose syrup.

The pharmacologically active compounds may be advantageously employed in a unit dosage of from 0.1 to 250 milligrams or more depending on the size of the animal. For example, a large animal such as a horse may require tablets of 500-1000 mg active ingredient. The unit dosage may be given a suitable number of times daily so that the daily dosage may vary from 0.3 to 450 milligrams. Five to 25 milligrams appears optimum per unit dose.

It is only necessary that the active ingredient constitute an effective amount, i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed. The exact individual dosages as well as daily dosages will, of course, be determined according to standard medical principles under the direction of a physician or veterinarian.

The active agents of the invention may be combined with other pharmacologically active agents, or with buffers, antacids or the like, for administration and the proportion of the active agent in the compositions may be varied widely.

The following are examples of compositions formed in accordance with this invention.

EXAMPLES 15A TO 15D

Capsules of 5 mg (Example 15A), 25 mg (Example 15B), and 50 mg (Example 15C) of active ingredient per capsule are prepared. With the higher amounts of active ingredient, adjustment may be made in the amount of lactose.

Typical blend for encapsulation	*Per capsule, mg.*
Active ingredient	5.0
Lactose	296.7
Starch	129.0
Magnesium stearate	4.3
Total	435.0 mg.

Additional capsule formulations preferably contain a higher dosage of active ingredient and are as follows.

Example 15D Ingredients	*Per capsule, mg.*
Active ingredient	25.0
Lactose	306.5
Starch	99.2
Magnesium stearate	4.3
Total	435.0 mg.

In each case, the selected active ingredient is uniformly blended with lactose, starch, and magnesium stearate and the blend is then encapsulated.

EXAMPLE 16

This is a typical formulation for a tablet containing 5.0 mg of active ingredient per tablet. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

	Per tablet, mg.
(1) Active ingredient	5.0
(2) Corn starch	13.6
(3) Corn starch (paste)	3.4
(4) Lactose	79.2
(5) Dicalcium phosphate	68.0
(6) Calcium stearate	0.9
	170.1 mg.

Ingredients 1, 2, 4 and 5 are uniformly blended. A 10 percent paste in water of ingredient 3 is prepared. The blend is granulated with the starch paste and the wet mass is passed through an eight mesh screen. The wet

granulation is dried and sized through a twelve mesh screen. The dried granules are blended with the calcium stearate and pressed.

EXAMPLE 17

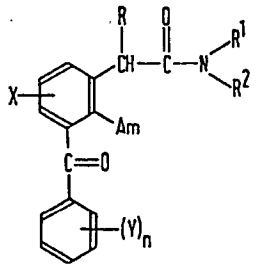
This is an example of an injectable - 2% sterile solution.

	Per cc.
Active ingredient	20 mg
Preservative, e.g. chlorobutanol	0.5% weight/volume
Water for injection	q.s.

The solution is prepared and clarified by filtration, filled into vials which are sealed and then autoclaved.

CLAIMS

1. A compound having the following formula referred to herein as formula I:



wherein:

R represents a hydrogen atom or a lower alkyl group;

R^1 and R^2 represent a hydrogen atom or a lower alkyl, cycloalkyl or phenyl group or a phenyl group substituted by a lower alkyl, lower alkoxy, nitro or trifluoromethyl group or a halogen atom; and R^1 and R^2 when taken together with the adjacent nitrogen atom form a heterocyclic residue:

X represents a hydrogen or a halogen atom or a lower alkyl, lower alkoxy, trifluoromethyl, lower alkylthio, lower alkyloxythio or lower alkyldioxythio group;

Am represents a primary amino ($-NH_2$), methylamino or dimethylamino group; and

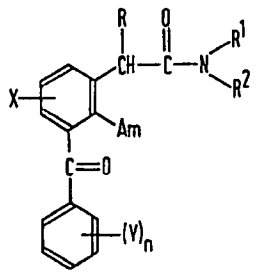
n is 1 to 3 inclusive.

2. 2-Amino-3-benzoyl-5-chlorophenylacetamide.
3. 2-Amino-3-benzoyl-phenylacetamide.
4. 2-Amino-3-(4-chlorobenzoyl)phenylacetamide.
5. 4-[2-(2-Amino-3-benzoylphenyl)acetyl]morpholine.
6. 2-Amino-3-benzoyl-N-methylphenylacetamide.
7. 2-Amino-3-benzoyl-N,N-dimethylphenylacetamide.
8. 2-Amino-3-(4-fluorobenzoyl)phenylacetamide.
9. 2-Amino-3-benzoyl-5-chloro-N-methylphenylacetamide.
10. A compound as claimed in any of Claims 1 to 9 for use in alleviating inflammation in a living animal body.
11. A compound as claimed in any of Claims 1 to 9 for use in producing an inhibitory effect on blood platelet aggregation.
12. A compound as claimed in any of Claims 1 to 9 for use in producing an analgetic effect in a living animal body.
13. A therapeutic composition comprising (a) an effective amount of a compound as claimed in any of Claims 1 to 9 and (b) a pharmaceutically acceptable carrier therefor.

New claims or amendments to claims filed on 19 Nov. 1980.
Superseded claims 1
New or amended claims:-

CLAIMS

1. A compound having the following formula referred to herein as formula I:



wherein:

R represents a hydrogen atom or a lower alkyl group;

R^1 and R^2 represent a hydrogen atom or a lower alkyl, cycloalkyl or phenyl group or a phenyl group substituted by a lower alkyl, lower alkoxy, nitro or trifluoromethyl group or a halogen atom; and R^1 and R^2 when taken together with the adjacent nitrogen atom form a heterocyclic residue;

X represents a hydrogen atom or a halogen atom or a lower alkyl, lower alkoxy, or trifluoromethyl group;

Y represents a hydrogen or a halogen atom or a lower alkyl, lower alkoxy, trifluoromethyl, lower alkylthio, lower alkyloxythio or lower alkyldioxythio group;

Am represents a primary amino ($-NH_2$), methylamino or dimethylamino group; and

n is 1 to 3 inclusive.

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